PROFESSIONAL INFORMATION LEAFLET FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

PROPRIETARY NAME (and dosage form)

DEGRANOL (tablet)

COMPOSITION

Each tablet contains:

Carbamazepine 200 mg.

Excipients: Magnesium stearate, maize starch, microcrystalline cellulose 101, polysorbate 80, purified talc and sodium starch glycollate.

Sugar-free.

PHARMACOLOGICAL CLASSIFICATION

A 2.5 Anticonvulsants, including antiepileptics.

PHARMACOLOGICAL ACTION

Carbamazepine possesses both anticonvulsant and psychotropic properties.

Pharmacodynamic properties

Carbamazepine limits the repetitive firing of action potentials evoked by a sustained depolarisation of mouse spinal cord or cortical neurons maintained *in vitro*.

Pharmacokinetic properties

Carbamazepine is absorbed slowly and erratically after oral administration. Peak concentrations in plasma are usually observed 4 to 8 hours after oral ingestion but may be delayed by as much as 24 hours, especially following the administration of a large dose. The medicine distributes rapidly into all tissues. Approximately 75 % of carbamazepine in the plasma binds to plasma proteins, and concentrations in the CSF appear to correspond to the concentration of free medicine in plasma. Carbamazepine crosses the placenta and is distributed into breast milk. It is metabolised in the liver by the CYP 450 enzyme system, to the active carbamazepine-10,11-epoxide and further to inactive metabolites. It is excreted mainly in the urine, with some excreted in faeces. Carbamazepine has a half-life of about 15 hours.

INDICATIONS

Epilepsy with motor and psychic manifestations:

- psychomotor or temporal-lobe epilepsy,
- grand mal (generalised tonic-clonic seizures),
- mixed forms of focal seizures.

DEGRANOL is also used in the treatment of:

- Acute mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence.
- Idiopathic trigeminal neuralgia.
- Idiopathic glossopharyngeal neuralgia.

DEGRANOL is suitable for both monotherapy and combination therapy. DEGRANOL is usually not effective in absence (petit mal) and myoclonic seizures.

CONTRAINDICATIONS

- Hypersensitivity to carbamazepine or structurally related medicines, e.g. tricyclic antidepressants, or any other component of the formulation.
- In patients with heart block.
- Concomitantly with a monoamine oxidase inhibitor or within 2 weeks of stopping such treatment.
- In patients with porphyria.
- DEGRANOL should not be used in patients with a history of bone marrow depression.
- DEGRANOL is contraindicated in pregnancy and lactation (see PREGNANCY AND LACTATION).
- In patients with a liver disease.

WARNINGS

Serious dermatologic reactions and HLA-B*1502 allele

Dangerous or even fatal dermatologic reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported, especially in patients with the inherited allelic variant HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Genetically at-risk patients should be screened prior to receiving DEGRANOL. DEGRANOL should not be started in patients who test positive for the allele.

Suicidal behaviour and ideation

Analysis of reports of suicidal behaviour or ideation has shown that antiepileptic medicines, including DEGRANOL, increase the risk of suicidal thoughts or behaviour in patients taking these medicines for any indication, when compared to placebo.

All patients who are currently taking or starting on DEGRANOL should be closely monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression.

Carcinogenicity

In rats treated with DEGRANOL for two years, the incidence of tumours of the liver was found to be increased. There is, however, no evidence to indicate that this observation has any significance relative to therapeutic use of DEGRANOL.

Hypersensitivity

DEGRANOL may trigger hypersensitivity reactions, including multi-organ hypersensitivity reactions, which can affect the skin, liver, haematopoietic organs and lymphatic system or other organs, either individually or together in the context of a systemic reaction. If signs and symptoms of hypersensitivity reactions occur, DEGRANOL should be withdrawn.

Seizures

DEGRANOL should be used with caution in patients with mixed seizures, which includes absences, either typical or atypical. In all these conditions, DEGRANOL may exacerbate seizures. In the event of exacerbation of seizures, DEGRANOL should be discontinued.

Hepatic function

Liver function tests should also be undertaken periodically. If allergic skin reactions occur, if the platelet count diminishes, if tests reveal deterioration in liver function, or if any serious adverse symptoms develop, DEGRANOL should be withdrawn.

Withdrawal

DEGRANOL should be withdrawn gradually to minimise the potential of increased seizure frequency.

INTERACTIONS

Cytochrome P4503A (CYP3A4) is the main enzyme catalysing formation of the active metabolite carbamazepine-10,11-epoxide. Co-administration of inhibitors of CYP3A4 may result in increased plasma concentrations which could induce adverse reactions. Co-administration of CYP3A4 inducers might increase the rate of DEGRANOL metabolism, thus leading to a potential decrease in carbamazepine serum level and potential decrease in the therapeutic effect.

DEGRANOL is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver and may therefore reduce plasma concentrations of co-medications mainly metabolised by CYP3A4 by induction of their metabolism.

Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11-epoxide. Co-administration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11-epoxide plasma concentrations. Such inhibitors are valproic acid, valpromide, valnoctamide and progabide.

Agents that may raise carbamazepine and/or carbamazepine-10,11-epoxide plasma levels:

Analgesics, non-steroidal anti-inflammatory medicines (NSAIDs): ibuprofen.

Androgens: danazol.

Antibiotics: macrolide antibiotics: erythromycin, clarithromycin.

Antidepressants: fluoxetine, fluvoxamine.

Antiepileptics: vigabatrin.

Antifungals: itraconazole, ketoconazole, fluconazole, voriconazole.

Antihistamines: loratadine.

Antipsychotics: olanzapine, quetiapine.

Antituberculosis: isoniazid.

Carbonic anhydrase inhibitors: acetazolamide.

Cardiovascular medicines: diltiazem, verapamil.

Gastrointestinal medicines: cimetidine, omeprazole.

Muscle relaxants: oxybutynin, dantrolene.

Other interactions: nicotinamide (in adults, only in high dosages).

Quetiapine, primidone and valproic acid were reported to increase concentration of the active metabolite carbamazepine-10,11-epoxide.

Agents that may decrease carbamazepine and/or carbamazepine-10,11-epoxide plasma levels:

The dose of DEGRANOL may have to be adjusted when used concomitantly with the substances described below.

Antiepileptics: oxcarbazepine, phenobarbitone, phenytoin, primidone, and, although the data are partly contradictory, possibly also clonazepam or valproic acid.

Antineoplastics: cisplatin or doxorubicin.

Antituberculosis: rifampicin.

Bronchodilators or anti-asthma medicines: theophylline, aminophylline.

Dermatological medicines: isotretinoin.

Other interactions: herbal preparations containing St John's wort *(Hypericum perforatum).*

Effect of DEGRANOL on plasma levels of concomitant agents:

DEGRANOL may lower the plasma level, diminish or even abolish the activity of certain medicines. The dosage of the following medicines may have to be adjusted to clinical requirements:

Analgesics: methadone, paracetamol, phenazone (antipyrine).

Antibiotics: doxycycline.

Anticoagulants: oral anticoagulants (e.g. warfarin).

Antidepressants: bupropion, citalopram, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine).

Antiepileptics: clobazam, clonazepam, ethosuximide, lamotrigine, primidone, topiramate, valproic acid.

Plasma phenytoin levels have been reported both to be raised and to be lowered by DEGRANOL, and there have been rare reports of an increase in plasma mephenytoin levels.

Antineoplastics: imatinib.

Antipsychotics: clozapine, haloperidol and bromperidol, quetiapine.

Anxiolytics: alprazolam.

Bronchodilators or anti-asthma medicines: theophylline.

Contraceptives: hormonal contraceptives (alternative contraceptive methods should be considered).

Cardiovascular medicines: calcium channel blockers (dihydropyridine group) e.g. felodipine, digoxin.

Corticosteroids: prednisolone, dexamethasone.

Immunosuppressants: ciclosporin, everolimus.

The level of serum folic acid should be observed during anticonvulsant therapy since DEGRANOL may enhance the metabolism of folic acid.

Combinations to be taken into consideration:

Concomitant use of DEGRANOL and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

Combined use of DEGRANOL and lithium, or metoclopramide on the one hand and DEGRANOL and neuroleptics (haloperidol, thioridazine) on the other, may lead to increased neurological adverse reactions (with the latter combination even in the presence of therapeutic plasma levels).

Concomitant medication with DEGRANOL and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia.

DEGRANOL may antagonise the effects of non-depolarising muscle relaxants (e.g. pancuronium); their dosage may need to be raised, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.

DEGRANOL may reduce the patient's alcohol tolerance; it is therefore advisable to abstain from alcohol during treatment.

PREGNANCY AND LACTATION

Pregnancy:

Safety of DEGRANOL in pregnancy has not been demonstrated.

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. Congenital malformations have been reported in infants born to women given DEGRANOL during pregnancy. There are reports of developmental disorders and malformations, including spina bifida and hypospadias in association with DEGRANOL (see CONTRAINDICATIONS).

Women of childbearing potential:

If pregnancy occurs in a woman receiving DEGRANOL or if the problem of initiating treatment with DEGRANOL arises during pregnancy, the potential benefits of DEGRANOL must be carefully weighed against its possible hazards, particularly in the first three months of pregnancy (see CONTRAINDICATIONS).

In women of childbearing age DEGRANOL should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic medicines is greater than in those of mothers receiving the individual medicines as monotherapy.

Lactation

The active substance of DEGRANOL passes into breast milk. Safety in breastfeeding has not been demonstrated. Excessive somnolence and allergic skin reactions have been reported in breastfed children (see CONTRAINDICATIONS).

Fertility

There have been reports of impaired male fertility and/or abnormal spermatogenesis (see SIDE EFFECTS).

DOSAGE AND DIRECTIONS FOR USE

Trigeminal neuralgia

An initial dose of 200 mg twice daily gradually increasing until a suitable response is obtained. The usual dosage required is one tablet three or four times daily.

In elderly or hypersensitive patients an initial dose of half a tablet (100 mg) twice daily is recommended.

Epilepsy

Adults:

Initially 100 mg to 200 mg once or twice daily, followed by a slow increase until usually, at a level of 400 mg twice or three times a day, the best response is obtained. In some instances 1 600 mg in three to four divided doses may be necessary.

Children:

Administered in several fractional doses, usually 10 to 20 mg/kg per day.

5 to 10 years: 400 to 600 mg (2 to 3 tablets) per day.

10 to 15 years: 600 to 1 000 mg (3 to 5 tablets) per day.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

Blood and the lymphatic system disorders

Frequent: Leukopenia, eosinophilia, thrombocytopenia

Less frequent: Acute intermittent porphyria, agranulocytosis, aplastic anaemia, haemolytic anaemia, variegate porphyria, folic acid deficiency, leukocytosis, pancytopenia, reticulocytosis

Immune system disorders

Less frequent: Lymphadenopathy, splenomegaly, a delayed multiorgan hypersensitivity disorder with fever and rashes, aseptic meningitis, anaphylactic reaction, angioedema

Endocrine disorders

Frequent: Oedema, fluid retention, weight increase, hyponatraemia

Less frequent: Abnormal thyroid function tests, bone metabolism disorders, galactorrhoea, gynaecomastia

Psychiatric disorders

Less frequent: Hallucinations, depression, anorexia, restlessness, aggression, agitation, activation of psychosis

Nervous system disorders

Frequent: Clumsiness or ataxia, confusion, dizziness, nystagmus, somnolence, headache

Less frequent: Paraesthesia, dystonias and dyskinesias with asterixis, aseptic meningitis, encephalopathy, neurotoxicity, malaise, myoclonus and trembling (see INTERACTIONS)

Frequency unknown: Drowsiness

Eye disorders

Less frequent: Glaucoma, conjunctivitis

Frequency unknown: Disorders of visual accommodation, diplopia

Ear and labyrinth disorders

Less frequent: Tinnitus, hypercusis, change in pitch perception

Cardiac disorders

Less frequent: Atrioventricular block, cardiac dysrhythmias, bradycardia,congestive heart failure, eosinophilic myocarditis, hypersensitivity, syncope, left ventricular failure, thromboembolism, thrombophlebitis, hypertension and hypotension

Respiratory, thoracic and mediastinal disorders

Less frequent: Pneumonitis, pneumonia, dyspnoea

Gastrointestinal disorders

Frequent: Nausea, vomiting, dry mouth

Less frequent: Pancreatitis, abdominal pain, diarrhoea or constipation, glossitis, stomatitis, loss of appetite

Hepato-biliary disorders

Frequent: Increased gamma-GT, increased blood alkaline phosphatase

Less frequent: Increased transaminases, hepatitis, cholestatic jaundice, granulomatous hepatitis

Skin and subcutaneous tissue disorders

Frequent: Allergic dermatitis, urticaria

Less frequent: Stevens-Johnson syndrome, toxic epidermal necrolysis, generalised erythematous rash, photosensitivity reactions, alopecia, exfoliative dermatitis, erythema multiforme, systemic lupus erythematosus, altered skin pigmentation, pruritus, acne, hyperhydrosis

Musculoskeletal, connective tissue and bone disorders

Less frequent: Arthralgia, muscle pain, muscle spasms

Renal and urinary disorders

Less frequent: Renal failure, interstitial nephritis, renal impairment, acute oliguria with proteinuria, urinary frequency and retention

Reproductive system and breast disorders

Less frequent: Sexual dysfunction/impotence, spermatogenesis

SPECIAL PRECAUTIONS

Medical supervision during treatment is essential.

Abnormalities of liver function and jaundice have been associated with long-term treatment.

Blood counts and liver function tests should be performed before commencing treatment.

Blood counts should then be repeated at weekly intervals during the first month of treatment and subsequently at monthly intervals. Liver function tests should also be undertaken periodically. If allergic skin reactions occur, if the leucocyte and/or platelet count diminishes, if tests reveal deterioration in liver function or if any serious adverse symptoms develop, DEGRANOL should be withdrawn (see WARNINGS).

Hyponatraemia due to the antidiuretic effect of DEGRANOL, possibly accompanied by vomiting, headache and mental confusion, has been observed.

A wide variety of other central nervous system, gastrointestinal, cardiovascular and dermatological effects have also been reported.

In patients with cardiovascular diseases, or with hepatic or renal disorders, glaucoma and in elderly patients, DEGRANOL should be administered with caution.

Tolerance may develop to some of the adverse effects of DEGRANOL and they can be minimised by a gradual increase in dosage and adjustment of maintenance dosage.

If treatment with DEGRANOL is withdrawn abruptly, the change-over to another antiepileptic medicine should be effected under cover of diazepam or a barbiturate.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Reaction time may be increased by DEGRANOL. The patient's safety as a road user or operator of machines may be impaired in consequence.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of overdosage:

Agitation, tremor, abnormal reflexes, convulsions, impairment of consciousness, hypertension or hypotension, nausea, vomiting, renal insufficiency, deep sleep, coma, EEG and ECG changes.

Treatment of overdosage:

There is no specific antidote.

The stomach should be emptied by aspiration and lavage.

Ensure clear airway and maintain respiration.

Treatment is mainly supportive and symptomatic.

Measures to monitor and safeguard vital functions.

Administration of diazepam where necessary.

IDENTIFICATION

A white round, flat tablet, with bevelled edges, plain on the one side and bisected on the other.

PRESENTATION

100 or 500 tablets are packed in a white polypropylene container and sealed with a white low density polyethylene cap together with a white foam or rayon insert.

56 or 84 tablets are packed in metallised lay flat bags which is composed of metallised polyester/laminant/ opaque white linear low density polyethylene.

56 or 84 tablets are packed in Ziplock layflat linear low density polyethylene bags with a key profile zipper and ribbed flanges.

Tablets are packed in clear polyvinylchloride blister strips sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C away from moisture.

Keep in original packaging until required for use

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

G/2.5/220

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration: 07 April 1975

Date of the most recent amendment to the professional information as approved by the Authority:

19 April 2020

Namibia: NS2 90/2.5/00879

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 188 088

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